60th Medical Group (AMC), Travis AFB, CA

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)

FINAL REPORT SUMMARY

(Please type all information. Use additional pages if necessary.)

PROTOCOL #: FDG20150022A **DATE:** 5 April 2016

PROTOCOL TITLE: "Pilot study of the pharmacokinetics (PK) and pharmacodynamics (PD) of Tranexamic Acid (TXA) in a Swine (Sus scrofa) and Sheep (Ovis aries) Model."

PRINCIPAL INVESTIGATOR (PI) / TRAINING COORDINATOR (TC): Maj Neff

DEPARTMENT: Surgery **PHONE #:** 423-5179

INITIAL APPROVAL DATE: 21 May 2015 **LAST TRIENNIAL REVISION DATE:** N/A

FUNDING SOURCE: AF Surgeon General

1. **RECORD OF ANIMAL USAGE:**

Animal Species:	Total # Approved	# Used this FY	Total # Used to Date
Sus scrofa	**3**	**3**	**3**
Ovis aries	**3**	**3**	**3**

2. **PROTOCOL TYPE / CHARACTERISTICS:** (Check all applicable terms in **EACH** column)

___ Training: Live Animal	___ Medical Readiness	___ Prolonged Restraint
___ Training: non-Live Animal	___ Health Promotion	___ Multiple Survival Surgery
__X_ Research: Survival (chronic)	___ Prevention	___ Behavioral Study
___ Research: non-Survival (acute)	___ Utilization Mgt.	___ Adjuvant Use
___ Other ( )	__X_ Other (Treatment)	___ Biohazard

3. **PROTOCOL PAIN CATEGORY (USDA):** (Check applicable) ___ C _X_ D ___ E

4. **PROTOCOL STATUS:**

***Request Protocol Closure:**

___ Inactive, protocol never initiated

___ Inactive, protocol initiated but has not/will not be completed

_X_ Completed, all approved procedures/animal uses have been completed

5. **Previous Amendments:**
List all amendments made to the protocol. **IF none occurred, state NONE. Do not use N/A.**

For the Entire Study Chronologically

Amendment Number	Date of Approval	Summary of the Change
None		

6. **FUNDING STATUS:** Funding allocated: $12,600 Funds remaining: $ 0

7. **PROTOCOL PERSONNEL CHANGES:**

Have there been any personnel/staffing changes (PI/CI/AI/TC/Instructor) since the last IACUC approval of protocol, or annual review? ___ Yes __X_ No

If yes, complete the following sections (Additions/Deletions). For additions, indicate whether or not the IACUC has approved this addition.

ADDITIONS: (Include Name, Protocol function - PI/CI/AI/TC/Instructor, IACUC approval - Yes/No)

DELETIONS: (Include Name, Protocol function - PI/CI/AI/TC/Instructor, Effective date of deletion)

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8. **PROBLEMS / ADVERSE EVENTS:** Identify any problems or adverse events that have affected study progress. Itemize adverse events that have led to unanticipated animal illness, distress, injury, or death; and indicate whether or not these events were reported to the IACUC.

None.

9. **REDUCTION, REFINEMENT, OR REPLACEMENT OF ANIMAL USE:**

REPLACEMENT (ALTERNATIVES): Since the last IACUC approval, have alternatives to animal use become available that could be substituted in this protocol without adversely affecting study or training objectives?

No.

REFINEMENT: Since the last IACUC approval, have any study refinements been implemented to reduce the degree of pain or distress experienced by study animals, or have animals of lower phylogenetic status or sentience been identified as potential study/training models in this protocol?

No.

REDUCTION: Since the last IACUC approval, have any methods been identified to reduce the number of live animals used in this protocol?

No.

10. **PUBLICATIONS / PRESENTATIONS:** (List any scientific publications and/or presentations that have resulted from this protocol. Include pending/scheduled publications or presentations).

Submitted to Shock, February 2016.

11. **Were the protocol objectives met, and how will the outcome or training benefit the DoD/USAF?**

Yes. This protocol provided a surgery resident with a easily accomplished, yet substantial project. The findings will directly address a military medical operational need.

12. **PROTOCOL OUTCOME SUMMARY:** (Please provide, in "ABSTRACT" format, a summary of the protocol objectives, materials and methods, results - include tables/figures, and conclusions/applications.)

A PILOT STUDY OF THE PHARMACOKINETICS OF TRANEXAMIC ACID VIA INTRAMUSCULAR AND INTRAOSSEOUS ADMINISTRATION IN TWO NON-HEMORRHAGE ANIMAL MODELS

INTRODUCTION: Tranexamic acid (TXA) has been shown in a to reduce blood loss following surgery and may provide a mortality benefit in trauma patients. The addition of TXA to trauma transfusion protocols is now standard practice in many civilian and military sectors. TXA is routinely administered by the intravenous (IV) route and has been shown to be most effective when given within 3 hours of injury. However, in a field setting establishing IV

access can be difficult and limited, so we examined the pharmacokinetics (PK) of TXA administered to pigs and sheep by intraosseous (IO) and intramuscular (IM) routes, compared to the IV route.

MATERIALS AND METHODS: Two cohorts of 3 pigs and sheep were administered one gram TXA by the IV, IM or IO route, respectively. Twelve serum samples were obtained over a 6-hour period, and TXA concentrations were determined by gas chromatography, time-of-flight, and mass spectrometry. Traditional compartmental PK modeling was performed to determine drug pharmacokinetics.

RESULTS: Plots of TXA concentrations in serum from pigs are shown in figure 1, which demonstrates that the curves are similar for IV, IO and IM routes. There were differences in bioavailability depending on route and species, and the drug half-life was shorter in pigs, compared to sheep. No thrombotic events were observed, however the sheep that received IO TXA did experience mild hematuria immediately after administration, which resolved spontaneously.

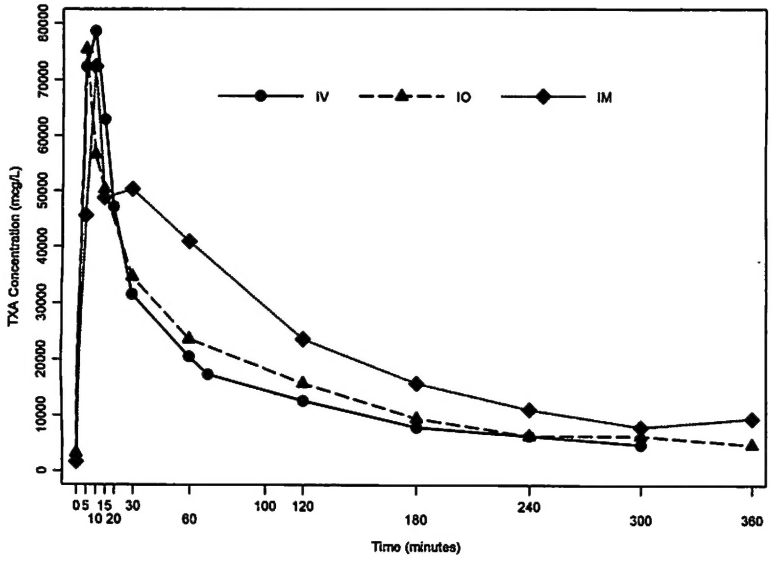

Figure 1. TXA concentrations in pig serum for IV, IO, and IM routes of injection.

CONCLUSIONS: Based on this pilot study, TXA delivered by IO and IM routes has potential to be a viable alternative to IV administration. Investigations should be expanded to human studies to further explore these alternative routes of administration of TXA. More data is needed to determine ideal dosages via these novel routes as well as the bioavailability profile during ongoing hemorrhage.

(PI / TC Signature)

4/22/16
(Date)

Attachments:
Attachment 1: Defense Technical Information Center (DTIC) Abstract Submission **(Mandatory)**

Attachment 1
Defense Technical Information Center (DTIC) Abstract Submission

This abstract requires a brief (no more than 200 words) factual summary of the most significant information in the following format: Objectives, Methods, Results, and Conclusion.

INTRODUCTION: TXA is routinely administered by the intravenous (IV) route. However, in a field setting establishing IV access can be difficult, so we examined the pharmacokinetics of TXA administered to pigs and sheep by intraosseous (IO) and intramuscular (IM) routes, compared to the IV route.
MATERIALS AND METHODS: Two cohorts of 3 pigs and sheep were administered one gram TXA by the IV, IM or IO route, respectively. Twelve serum samples were obtained over a 6-hour period, and TXA concentrations were determined. Traditional compartmental PK modeling was performed to determine drug pharmacokinetics.
RESULTS: Plots of TXA concentrations in serum from pigs and sheep demonstrated that the curves are similar for IV, IO and IM routes. There were differences in bioavailability depending on route and species, and the drug half-life was shorter in pigs, compared to sheep.
CONCLUSIONS: Based on this pilot study, TXA delivered by IO and IM routes has potential to be a viable alternative to IV administration. Investigations should be expanded to human studies to further explore these alternative routes of administration of TXA. More data is needed to determine ideal dosages via these novel routes as well as the bioavailability profile during ongoing hemorrhage.

Grant Number:_____
From:_____
****If you utilized an external grant, please provide Grant # and where the grant came from. Thank you.**